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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,486	11/16/2000	Christopher Joseph Schofield	P02005US0	3471

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EXAMINER

BORIN, MICHAEL L

ART UNIT PAPER NUMBER

1631

DATE MAILED: 02/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/582,486	<b>Applicant(s)</b> SCHOFIELD ET AL.	
	<b>Examiner</b> Michael Borin	<b>Art Unit</b> 1631	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.**

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 October 2003.  
 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.  
 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-227 is/are pending in the application.  
     4a) Of the above claim(s) 1-11, 13, 15-36, 38, 41-51, 53, 54, 56 and 59-227 is/are withdrawn from consideration.  
 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
 6) ☒ Claim(s) 12, 14, 37, 39, 40, 52, 55, 57 and 58 is/are rejected.  
 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.  
 10) ☒ The drawing(s) filed on 23 June 2000 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
     a) ☒ All    b) ☐ Some \*    c) ☐ None of:  
         1. ☒ Certified copies of the priority documents have been received.  
         2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
         3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
     \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>06/23/2000</u> . | 6) <input type="checkbox"/> Other: _____  |

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## **DETAILED ACTION**

### ***Status of Claims***

1. Claims 1-227 are pending.
2. Applicant's treatment of status of claims is confusing. In communication filed 05/16/2003, applicant indicates on p. 10, line 4, that claims 15-27 are canceled, although they remain in pending status in the list of claims. Please clarify.
3. Response to restriction requirement filed 05/16/2003 and 10/21/2003 are acknowledged. Applicant elected, with traverse, Group IV. Applicant does not traverse restriction of Groups I-III, VI-VIII (claims 1-11, 17-25), but argues that Group IV and V should be rejoined as they both address DAOCS which has modified binding site for penicillin N. Examiner disagrees. First, claims of Groups IV and V do not recite DAOCS which has modified binding site for penicillin N, because the claims have been amended to exclude binding site for penicillin N, and are rather drawn to DAOC binding site. Second, claims 12 and 13 address DAOCS with modifications at different binding sites: side chain binding site of DAOC, and penicillin/cephalosporin binding site of DAOC, respectively. There is nothing on record suggesting that these sites are the same; contrary, they are discussed as separate embodiments in the specification (pages 6-7, and page 8, respectively). Consequently the claims are

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treated as drawn to structurally different products. The restriction requirement is still deemed proper and is therefore made FINAL.

4. As per election of species, applicant elected DAOCS with modification of Leu158 residue.

***Further restriction***

5. In addition, the added and amended claims are directed to inventions that are independent or distinct from the invention originally claimed for the following reasons: The claims address several sites in DAOCS that are being modified: side chain binding site of DAOC, side chain binding site of penicillin N, penicillin/cephalosporin binding site, region 300-311. Various permutations of said modified sites are addressed in different groups of claims as follows <sup>1</sup>:

- IV. Claims 12,14,37,39,40,52,55,57,58 drawn to enzyme having similarity to DAOCS with modified side chain binding site of DAOC and modified Leu158 (elected species).
- V. Claims 13,42-46,49,51,53,60-64, drawn to Enzyme having similarity to DAOCS with modified penicillin/cephalosporin binding site

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<sup>1</sup>Numeration of groups continues after grouping of claims presented in the initial restriction requirement.

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- X. Claims 15,47,48,50,65,66 drawn to Enzyme having similarity to DAOCS with modifications at both side chain binding site of DAOC and penicillin/cephalosporin binding site.
- XI. Claims 38,56 drawn to Enzyme having similarity to DAOCS with modified side chain binding site of DAOC and modified region 300-311<sup>2</sup>.
- XII. Claim 41 drawn to Enzyme having similarity to DAOCS with modified side chain binding site of penicillin N and modified region 300-311.

Inventions of Groups IV, V, X, XI are structurally and functionally different products which are made by different methods and have different uses. The examination of the Groups will require different searches of the US Patents and scientific literature and would require consideration of different patentability issues. Since applicant has elected Group IV, claims 1-11, 13, 15-36,38,41-51,53,54,56,59-~~66~~<sup>227</sup> are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected groups.

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<sup>2</sup> Note, that unlike Group IV, Group X does not address additional modification at residues including Leu158, which is the elected embodiment.

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Claims 12,14,37,39,40,52,55,57,58 are examined on merit to the extent they read on elected species: Enzyme having similarity to DAOCS with modified side chain binding site of DAOC and modified Leu158.

***Information Disclosure Statement***

6. Applicants' Information Disclosure Statement filed 06/23/2000 has been received and entered into the application. Accordingly, as reflected by the attached completed copies of forms PTO-1449, the cited references have been considered.

***Drawings***

7. The subject matter of this application admits of illustration by a drawing to facilitate understanding of the invention. It is noted that Figure 2 does not correspond to the description of drawing; the latter addresses structures A and B which are not depicted on the Figure. No new matter may be introduced in the required drawing.

Applicants are required to submit drawing correction within the time period set for responding to this Office action. Failure to respond to this requirement may result in abandonment of the instant application or in a notice of failure to fully respond to this Office action.

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***Sequence Listing***

8. The Sequence Listing was approved by STIC for matters of form.
9. This application contains sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to identify sequences present in the disclosure by their SEQ ID number. Applicant must provide an amendment identifying sequence presented on p. 11.

***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 12,14,37,39,40,52,55,57,58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons:
  - A. Claims 12,14,37,39,40,52,55,57,58 are drawn to an enzyme which has "significant sequence similarity" to DAOC synthetase (DAOCS) and which has two

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modifications in its structure. The claims do not specify whether the modifications are to be done in DAOCS itself or in protein which has significant sequence similarity to DAOCS. Consequently, the claims are vague and indefinite in regard to the structure of the product being claimed.

B. Claims 12,14,37,39,40,52,55,57,58 are drawn to an enzyme which has "significant sequence similarity" to DAOC synthetase (DAOCS) which has modifications in side chain binding site of DAOC. As the binding site that binds side chain of DAOC is not defined in the specification, it is not clear what part of the enzyme is being modified. Accordingly, it is not possible to define the metes and bounds of the subject matter that will be protected by the patent grant .

C. At claim 12, the phrase "significant sequence similarity" is indefinite because it is a relative term, but no standard of reference has been provided with which to determine what degree of similarity is considered as significant. Accordingly, it is not possible to determine what proteins are embraced within the scope of the claim.

D. Claims 40,52,55,57,58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to Enzyme having similarity to DAOCS which have mutations that "create or delete a binding



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interaction". It is not possible to define the metes and bounds of the subject matter of the claims because it is not clear, first, what "interactions" are meant, and, second, what mutations are related to creation of these unidentified binding interaction or deletion of a binding interaction.

***Claim Rejections - 35 USC § 112, first paragraph (enablement)***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 12,14,37,39,40,52,55,57,58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is applied for the following reasons.

The claims are directed to an enzyme which has "significant sequence similarity" to DAOC synthetase wherein there are two modifications in structure:

- 1) the site chain binding site of DAOC is modified, and
- 2) one or more of sixteen residues is changed or deleted. Out of these sixteen residues, Leu158 is currently addressed as the elected species.

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One skilled in the art could not make the invention with the claimed breadth without an undue amount of experimentation because:

1) As discussed in rejection under 35 U.S.C. 112, second paragraph, above (paragraph 10.A), it is not clear whether the claims address modifications in DAOCS itself or of some other enzyme that has "significant sequence similarity" to DAOCS;

2) The claims require the binding site that binds side chain of DAOC to be modified. However, the structure of this binding site is not defined. Specification address modifications of several residues (p. 7) but these are the residues that, according to the claims, must be changed in addition to the unidentified binding site that binds side chain of DAOC.

3) In regard to modification of Leu158, which is a hydrophobic residue itself, all the guidance present in specification is to "usefully modify it to more hydrophobic character". As no further guidance is present, it is not clear what product is intended to be made.

4) Further, in regard to 40,52,55,57,58 drawn to enzyme in which mutations are introduced to "create or delete a binding interaction", there is no guidance on what mutations will yield added binding interactions, and, contrary, what mutations will result in product with deleted binding interactions.

Consequently, an artisan would not know how to make the product as claimed.

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12. Further, one skilled in the art would not be able to use the invention as claimed without an undue amount of experimentation because the claims are directed to an enzyme which has "significant sequence similarity" to DAOC synthetase wherein said enzyme has a number of unidentified modifications in its structure. It is not possible to predict the effect of replacing or deleting a single amino acid residue on peptide's structure or bioactivity. The amino acid sequence of the peptide is of great importance in determining the secondary and tertiary structures of the peptide. This is because the peptide's structure is determined by the interplay of the hydrophobic/hydrophilic, steric and electrostatic forces among the linked amino acid residues. Therefore, changing a single residue alters these forces unpredictably, and impose a new unpredictable structure of the modified peptide. Therefore, if replacing one or more residues in a peptide unpredictably alters its structure, this replacement also may alter bioactivity unpredictably. The specification does not provide any guidance on how to modify the site chain binding site of DAOC. In fact, even the site chain binding site of DAOC itself is not defined. Specification address modifications of several residues (p. 7) but these are the residues that, according to the claims, must be changed in addition to the unidentified binding site that binds side chain of DAOC. Further, in regard to 40,52,55,57,58 drawn to enzyme in which mutations are introduced to "create or delete a binding interaction", there is no guidance on what remaining activity, if any, is expected from such product, what activity will arise

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from product with added binding interactions, and what activity will arise from product with deleted binding interactions. In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not use the invention with the claimed breadth without an undue amount of experimentation.

***Claim Rejections - 35 USC § 112, first paragraph (written description)***

13. Claims 12,14,37,39,40,52,55,57,58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to an enzyme which has "significant sequence similarity" to DAOC synthetase, the site chain binding site of DAOC is modified, and one or more of sixteen residues is changed or deleted (of these sixteen residues, Leu158 is currently addressed as the elected species).

The specification describes DAOCS, but fails to identify specifically what changes in its structure (if it is DAOCS which structure is to be modified; this also remains unclear) are within the scope of the claims.

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The unpredictability of ligand receptor binding is known in the art. . Additionally, the effects, *a priori*, of deletions or nonconservative substitutions which differ sterically and/or hydrophobically on substrate/ligand binding is unpredictable; for substrate/ligand binding is stereospecific for a peptide/protein of the proper conformation ie. three dimensional structure. Length and amino acid composition affects the three dimensional nature of a given protein.

With respect to adequate disclosure of the scope of the presently claimed generic, applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* U.S. Court of Appeals Federal Circuit ( CA FC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997 No. 96-1175 regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope, both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention*. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above ( for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Unlike *Lilly*, applicant does not have a single example of a modified enzyme within the scope of the presently claimed invention and thus does not provide even

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a single modified enzyme species in support of a potentially broad generic of different and nonexemplified sequences.

Like Lilly, applicant asserts that there is a means of obtaining these peptides; however, this is not relevant to the disclosure requirement in which the applicant must demonstrate possession of the claimed scope at the time of filing.

Accordingly, it is clear that applicant has not demonstrated possession of the scope of the presently claimed subject matter. In fact applicant, in the present case, unlike the Lilly case, *has failed to demonstrate even a single nonpeptide species within the scope of the presently claimed generic.* Accordingly, applicant is not in possession of the presently claimed invention.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 12,14,37,39,40,52,55,57,58 are rejected under 35 U.S.C. 102(b) as being anticipated by the following Accession Numbers of Database Pir\_76: S40253,

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A39204, S54101. The referenced sequences are sequences of DAOCS in which residue Leu158 and at least one residue in 300-311 are modified as compared to the sequence SEQ ID No. 1 of the instant invention, along with other multiple substitutions in the sequence. As such the references read on the broadly claimed enzyme which has significant sequence similarity to DAOCS wherein Leu158, and at least one residue in 300-311 region, and the site chain binding site of DAOC are modified. In regard to the latter modification of site chain binding site of DAOC, as the site itself is not identified in the instant disclosure, modifications in the referenced sequences are considered to be reading on the claimed limitation.

***Conclusion.***

15. No claims are allowed

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (571) 272-0722.

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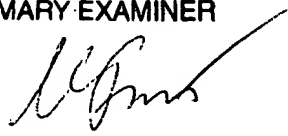
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Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0549.

February 12, 2004

MICHAEL BORIN, PH.D  
PRIMARY EXAMINER

mlb

A handwritten signature in black ink, appearing to read 'Michael Borin', with a long, sweeping horizontal stroke extending to the right.